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Influence of the SARS-CoV-2 outbreak on management and prognosis of new lung cancer cases, a retrospective multicenter real-life cohort study

Sonia Priou, MSc, Guillaume Lamé, PhD, Gérard Zalcman, MD, PhD, Marie Wislez, MD, PhD, Romain Bey, PhD, Gilles Chatellier, MD, PhD, Jacques Cadranel, MD, PhD, Xavier Tannier, PhD, Laurent Zelek, MD, PhD, Christel Daniel, MD, PhD, Christophe Tournigand, MD, PhD, Emmanuelle Kempf, MD, MSc, on behalf of the Assistance Publique – Hôpitaux de Paris (AP-HP) Cancer Group



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Influence of the SARS-CoV-2 outbreak on management and prognosis of new lung cancer cases, a retrospective multicenter real-life cohort study.

Sonia Priou, MSc (1,2), Guillaume Lamé, PhD (2), Gérard Zalcmán, MD, PhD (3), Marie Wislez, MD, PhD (4), Romain Bey, PhD (1), Gilles Chatellier, MD, PhD (5), Jacques Cadranel, MD, PhD (6), Xavier Tannier, PhD (7), Laurent Zelek, MD, PhD (8), Christel Daniel, MD, PhD (1,7), Christophe Tournigand, MD, PhD (9), Emmanuelle Kempf, MD, MSc (7,10) on behalf of the Assistance Publique – Hôpitaux de Paris (AP-HP) Cancer Group.

1. Assistance Publique – Hôpitaux de Paris, Innovation and Data, IT Department, Paris, France
2. Université Paris-Saclay, CentraleSupélec, Laboratoire Génie Industriel, Gif-sur-Yvette, France
3. Université de Paris, Assistance Publique – Hôpitaux de Paris, Department of thoracic oncology & Centre d'Investigation Clinique INSERM 1425, Bichat University Hospital, Paris, France
4. Université de Paris, Assistance Publique – Hôpitaux de Paris, Department of pneumology, Cochin Teaching Hospital, Paris, France
5. Université de Paris, Department of medical informatics, Assistance Publique Hôpitaux de Paris. Centre-Université de Paris (APHP-CUP), F-75015 Paris, France
6. Sorbonne Université, Assistance Publique – Hôpitaux de Paris, Service de Pneumologie et Oncologie thoracique, Hôpital Tenon and GRC04 Therascan Sorbonne Université, Paris, France
7. Sorbonne Université, Inserm, Université Sorbonne Paris Nord, Laboratoire d'Informatique Médicale et d'Ingénierie des Connaissances pour la e-Santé, LIMICS, Paris, France
8. Université de Seine Saint Denis, Assistance Publique – Hôpitaux de Paris, Department of thoracic oncology, Avicenne University Hospital, Paris, France
9. Université Paris Est Créteil, INSERM ; IMRB, Assistance Publique – Hôpitaux de Paris, Department of medical oncology, Henri Mondor and Albert Chenevier Teaching Hospital, Créteil, France

10. Université Paris Est Créteil, Assistance Publique – Hôpitaux de Paris, Department of medical oncology, Henri Mondor and Albert Chenevier Teaching Hospital, Créteil, France

Corresponding author:

Emmanuelle Kempf

Department of medical oncology,

Henri Mondor and Albert Chenevier Teaching Hospital,

Assistance Publique – Hôpitaux de Paris,

1 rue Gustave Eiffel

FR-94000 Créteil

Emmanuelle.kempf@aphp.fr

Phone: +33 (0)1 4981 4531 / France: +33 (01) 4981 2576

Abbreviation list:

AP-HP: Assistance Publique - Hôpitaux de Paris;

CDW: Clinical Data Warehouse;

ICD: International Classification of Diseases;

MTB: Multidisciplinary Tumor Board;

OS: Overall Survival

Abstract

Introduction: The SARS-CoV-2 pandemic has impacted the care of cancer patients. This study sought to assess the pandemic's impact on the clinical presentations and outcomes of newly referred patients with lung cancer from the Greater Paris area.

Methods: We retrospectively retrieved the electronic health records and administrative data of 11.4 million patients pertaining to Greater Paris University Hospital (AP-HP). We compared indicators for the 2018-2019 period to those of 2020 in regard to newly referred lung cancer cases. We assessed initial tumor stage, delay between first multidisciplinary tumor board (MTB) and anticancer treatment initiation, and 6-month overall survival (OS) rates depending on the anticancer treatment including surgery, palliative systemic treatment, and best supportive care (BSC).

Result: Among 6,240 patients with lung cancer, 2,179 (35%) underwent tumor resection, 2,069 (33%) systemic anticancer therapy, 775 (12%) BSC, whereas 1,217 (20%) did not receive any treatment. During the first lockdown, the rate of new diagnoses decreased by 32% compared with that recorded in 2018-2019. Initial tumor stage, repartition of patients among treatment categories, and MTB-related delays remained unchanged. The 6-month OS rates of patients diagnosed in 2018-2019 who underwent tumor resection were 98% vs. 97% (HR=1.2; 95% CI: 0.7-2.0) for those diagnosed in 2020; the respective rates for patients who underwent systemic anticancer therapy were 78% vs. 79% (HR=1.0; 95% CI: 0.8-1.2); these rates were 20% vs. 13% (HR=1.3; 95% CI: 1.1-1.6) for those who received BSC. COVID-19 was associated with poorer OS rates (HR=2.1; 95% CI: 1.6-3.0) for patients who received systemic anticancer therapy.

Conclusions: The SARS-CoV-2 pandemic has not exerted any deleterious impact on 6-month OS of new lung cancer patients that underwent active anticancer therapy in Greater Paris University hospitals.

Keywords (MeSH terms):

COVID-19, Delivery of Health Care, Early Cancer Detection, Lung Neoplasms, Quality of Health Care, Routinely Collected Health Data

Introduction

The SARS-CoV-2 pandemic has impacted the care trajectories of patients suffering from lung cancer, given that screening and lung nodule investigations were postponed¹. Due to potential delays in both diagnosis and treatment, modelers anticipated increasing lung cancer-related mortality rates in the forthcoming years². However, evidence of the pandemic's impact on care trajectories and outcomes of patients with lung cancer remains limited. Most published studies are small-sized, focused on the first 2020 semester only, and based on declarative surveys³.

This study sought to assess the impact of the SARS-CoV-2 pandemic on newly referred lung cancer cases from the Greater Paris area in regard to their tumor stage at diagnosis, anticancer upfront treatments, and 6-month overall survival (OS) during and after the SARS-CoV-2 epidemic outbreak in early 2020.

Material and Methods

We performed a retrospective cohort study using the Clinical Data Warehouse (CDW) of the Greater Paris University Hospitals (*Assistance Publique - Hôpitaux de Paris*, AP-HP), which contains routinely collected medical and administrative data pertaining to 11.4 million patients⁴. We selected patients with lung cancer who were newly referred to one of the 27 AP-HP teaching hospitals, with clinical data available. Patients were included provided that C33, C34, D021, or D022 ICD 10 codes were recorded between January 1, 2018 and December 31, 2020, that no recurrences were noted in the previous two years, and that these patients were not affected by another cancer.

We classified cancer treatments at AP-HP as follows: tumor resection including peri-operative treatment (codes GFFA001-002, GFFA004, GFFA006-013, GFFA015-016, GFFA018-019, GFFA021-031, GFFA033-034, and GFFC002 of the French Common Classification of Medical Procedures, 11th edition); systemic anticancer therapy including chemotherapy ICD-10 code Z511, irrespective of radiotherapy; either best supportive care (ICD-10 code Z515) or no cancer-related treatment.

Overall survival (OS) was defined as the time period between the date of the first occurrence of an ICD-10 lung cancer code and patient's death. The patient data were censored at the date the patient was last known to be alive. Patients' mortality follow-up ended on June 31, 2021, on account of the availability of out-of-hospital mortality data. The cohort definition permitted a minimum follow-up period of 6 months for all patients.

Rule-based natural language processing algorithms were used to identify the initial tumor stage using: 1/ baseline computer tomography (CT) text reports (90 days before up to 30 days after diagnosis date); 2/ first postoperative pathology report for resected tumors⁵. We classified the pTNM tumor stage (8th WHO TNM classification) according to the relapse risk into low- and high-risk defined as pT1-2aN0 and pT2b-T4 N0, xN1, pT1-2bN2, respectively. Based on identified Multidisciplinary Tumor Board (MTBs) dates, we calculated the time from first MTB to first anticancer treatment administration.

A positive recent polymerase chain reaction (PCR) serologic test for SARS-CoV-2 or one of the U071x ICD-10 codes from the cancer diagnosis date to the 1-year follow-up period defined SARS-CoV-2 infection. We compared the indicator values from the 2018–19 period with those of 2020, with a focus made on the French national lockdowns (March 17 to May 11, 2020; October 30 to December 15, 2020) periods. To compare the 2018-2019 data with those of 2020, Kaplan-Meier methodology was applied to estimate the cumulative probabilities of death from all causes, using a Cox proportional hazard model to estimate the hazard ratio (HR) with its 95% confidence intervals (CI) and p-values. Categorical variables were compared using Chi-squared testing.

This study was approved by the institutional AP-HP review board (IRB 00011591) (CSE 20-55_COVONCO-AP), and was in line with the French data privacy regulator (CNIL 1980120), as well.

Final data extraction was performed on February 1, 2022.

Results

Between January 2018 and December 2020, overall 6,240 patients with lung cancer were newly referred to an AP-HP hospital. In 2018, 2019, and 2020, the median age reached was 67 (IQR, 60 – 74), 68 (IQR, 60 – 75), and 68 (60-74) years, respectively. The rate of female patients was 37%, 40% and 38%, respectively. Among them, 2,179 (35%) underwent tumor resection, 2,069 (33%) received systemic anticancer therapy, 775 (12%) were given BSC, while

1,217 (20%), mostly managed at other centers than AP-PH hospitals, received either targeted therapies or no anticancer treatment at all at AP-HP. Main patient characteristics did not change over time (median age: 68 years; 38% of women). During the first national lockdown (March – May 2020), the number of new lung cancer diagnosis cases decreased by 32% compared with the average of the same months in 2018-2019 (587 vs. 401), with no catch-up observed afterwards (Fig 1.A) ⁴.

Among the 2,213 pathology reports available following tumor resection, overall 1,893 exhibited pTNM assessments. The distribution of pTNM risk groups did not change over time, being 62% vs. 64% for the low-risk and 38% vs. 36% for the high-risk categories in 2018-2019 vs. 2020, respectively ($p=0.40$). Among the 2,602 patients with baseline CT-scan reports available in the AP-HP CDW, the metastatic cancer rates did not change over time, being 29% vs. 28% in 2018-2019 and 2020, respectively ($p=0.78$). The rates of non-metastatic lung cancer patients undergoing tumor resection, non-surgical multimodal treatment, and BSC before vs. after the outbreak reached 42% vs. 42%, 49% vs. 50%, and 9% vs. 8%, respectively.

Among the 3,436 cases with a MTB report available in the AP-HP CDW, the median delay between the 1st MTB and 1st anticancer therapeutic procedure remained unchanged over time, including the lockdown-related time periods (Fig 2A and 2B).

The distribution of patients among each treatment category did not vary either over time (Fig 1.B). The 12-month OS rates among those who underwent tumor resection and systemic anticancer therapy were comparable in 2018-2019 vs. 2020 (98% vs. 97% [HR=1.2; 95% CI: 0.7-2.0]) and (78% vs. 79% [HR=1.0; 95% CI: 0.8-1.2]), whereas OS rates decreased in 2020 compared with 2018-2019 among patients receiving BSC (20% vs. 13% [HR=1.3; 95% CI: 1.1-1.6]) (Fig 3).

The SARS-CoV-2 infection rates among patients referred in 2020 were 23%, 16%, and 15% for the three abovementioned treatment categories. Among the patients diagnosed with COVID-19, the median time duration between the date of cancer diagnosis and date of Sars-Cov2 infection reached 68 days (IQR 14; 167). In this subpopulation, 8%, 18% and 75% were infected before, during, and after the hospital visit for the first administration of their anticancer treatment, respectively. Among patients referred in 2020 and undergoing tumor resection, OS rates were not significantly decreased in the SARS-CoV-2 group vs. the no COVID-19 group (HR=1.9; 95% CI: 0.7-5.2). Among patients referred in 2020 who received systemic anticancer therapy, OS was shorter in the SARS-CoV-2 group compared with the no COVID-19

group (HR=2.1, 95% CI: 1.5-3.0). Due to the limited number of patients in the BSC group, such an analysis could not be performed for this group.

Discussion

We observed a decrease in the number of patients with lung cancer newly referred to any AP-HP hospital during the first national COVID-19 lockdown, without any catch-up afterwards. This suggests that some patients might have been managed in other general hospitals and this, in an effort to avoid overloaded University hospitals during the COVID-19-related hospitalizations peaks. The transient interruption in lung cancer diagnostic procedures during the first wave likely accounts for the lower number of newly diagnosed patients¹. Of note, such a decrease was no longer observed during the second lockdown (Figure 1A). This suggests that both patients and healthcare providers adapted differently to that situation.

We did not identify any impairment in either initial clinical presentation or intent of anticancer therapeutic strategies concerning patients diagnosed during and after the SARS-CoV-2 outbreak, encompassing the surgical option, as well. Tumor stage shift related to the SARS-CoV-2 pandemic in lung cancer is under debate in the literature⁶. Some incidental new diagnoses might have been made at an early tumor stage during chest CT-scans related to COVID diagnostic procedures. Again, this suggests that patients presented no higher tumor burden due either delayed diagnosis, reported surgical decision, or both. Local guidelines emphasized the need to maintain an optimal access to tumor resection for patients diagnosed with lung or head and neck cancer at APHP during the pandemic.”

Like others, we found that the difference in the mortality rate of patients resected in 2018–19 vs. those of 2020 was not statistically significant^{6,7,8}. In the resected patient subgroup, the HR value was consistent with that observed in the other patient subgroups, with differences being not statistically significant, possibly due to a lack of power. Nevertheless, this association turned out to be statistically significant in a subgroup of resected patients with ongoing COVID-19, as previously reported in France⁹.

Similarly, survival of patients receiving systemic anticancer therapy was not likely to be significantly worse. However, in this category, patients referred in 2020 and presenting with a SARS-CoV-2 infection displayed a poorer survival than those without SARS-CoV-2 infection.

This observation is perfectly in line with the 30-43% COVID-19-related mortality rate in patients with lung cancer, as reported in previous studies ^{10,11}.

The mortality rate was significantly higher among patients receiving BSC in 2020 vs. those receiving it in 2018-2019. Advanced lung cancers have been recognized to be poor prognosticators in the event of SARS-CoV-2 infection ^{12,13}. Indeed, some authors reported that outbreak-related changes in care pathways impacted to a higher extent palliative therapies vs. curative ones, meaning surgery-based treatments ^{14,15}.

Considering this study's limitations, we had no access to the death causes of COVID-19 patients. A lead-time bias could account for the poorer survival in patients diagnosed after the SARS-CoV-2 outbreak ¹⁶.

Our results suggest that, although fewer patients were referred to the Greater Paris University Hospitals during the first lockdown, those who were treated did actually not experience a care trajectory and a clinical outcome that differed from that they would have undergone prior to the COVID-19 period. The additional mortality may have been more related to SARS-CoV-2 infection itself than to any treatment delays ¹⁷. However, longer follow-up periods are warranted to assess the pandemic's long-term impact on staging and anticancer therapeutic strategies of new lung cancer cases.

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Declaration of Interest statement

The authors have no conflict of interest to disclose.

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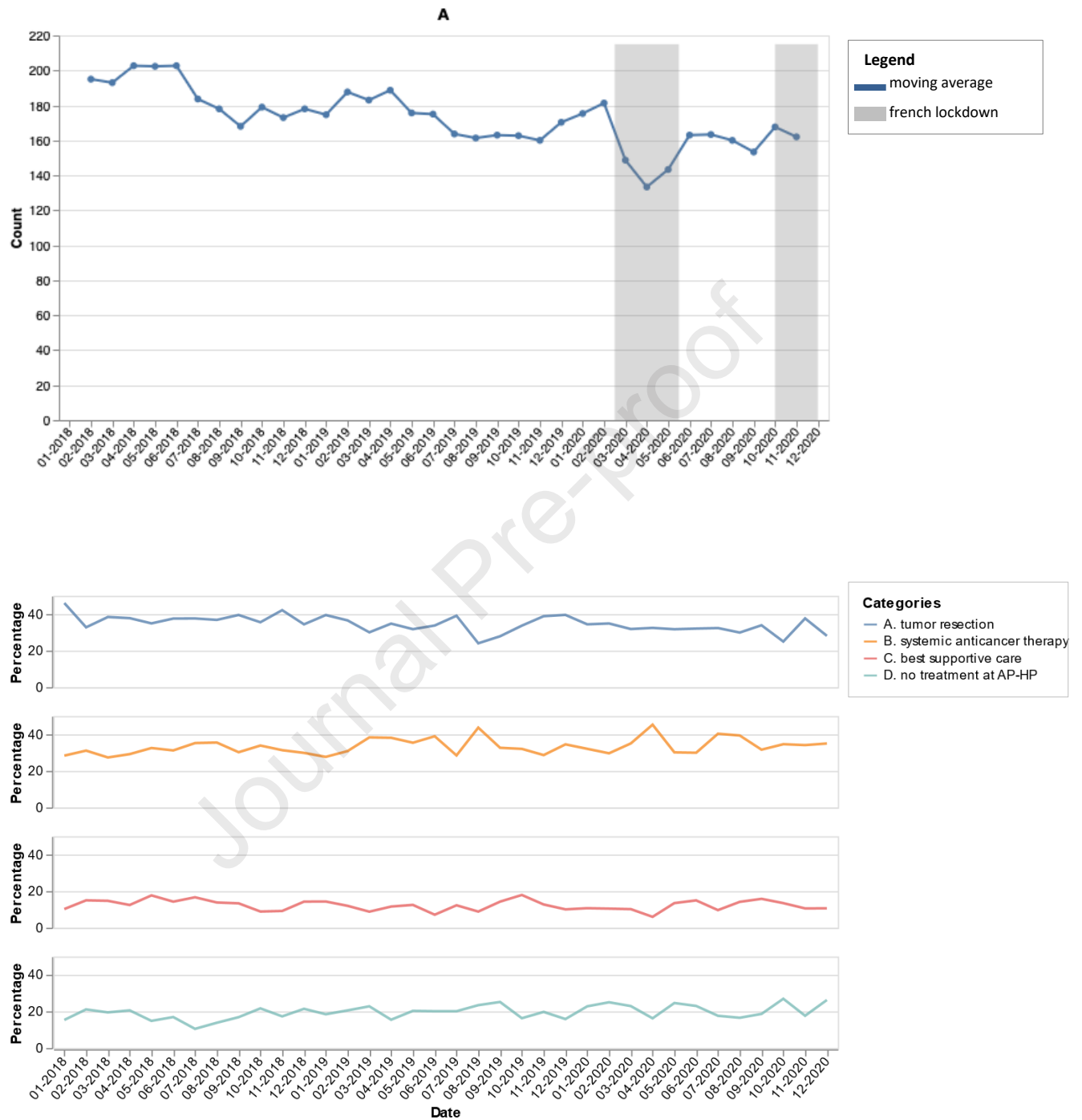


Figure 1. Three-point moving average of the monthly number of lung cancer cases newly referred to AP-HP teaching hospitals (1.A), and distribution of related upfront therapeutic strategies between 2018 and 2020 (1.B)

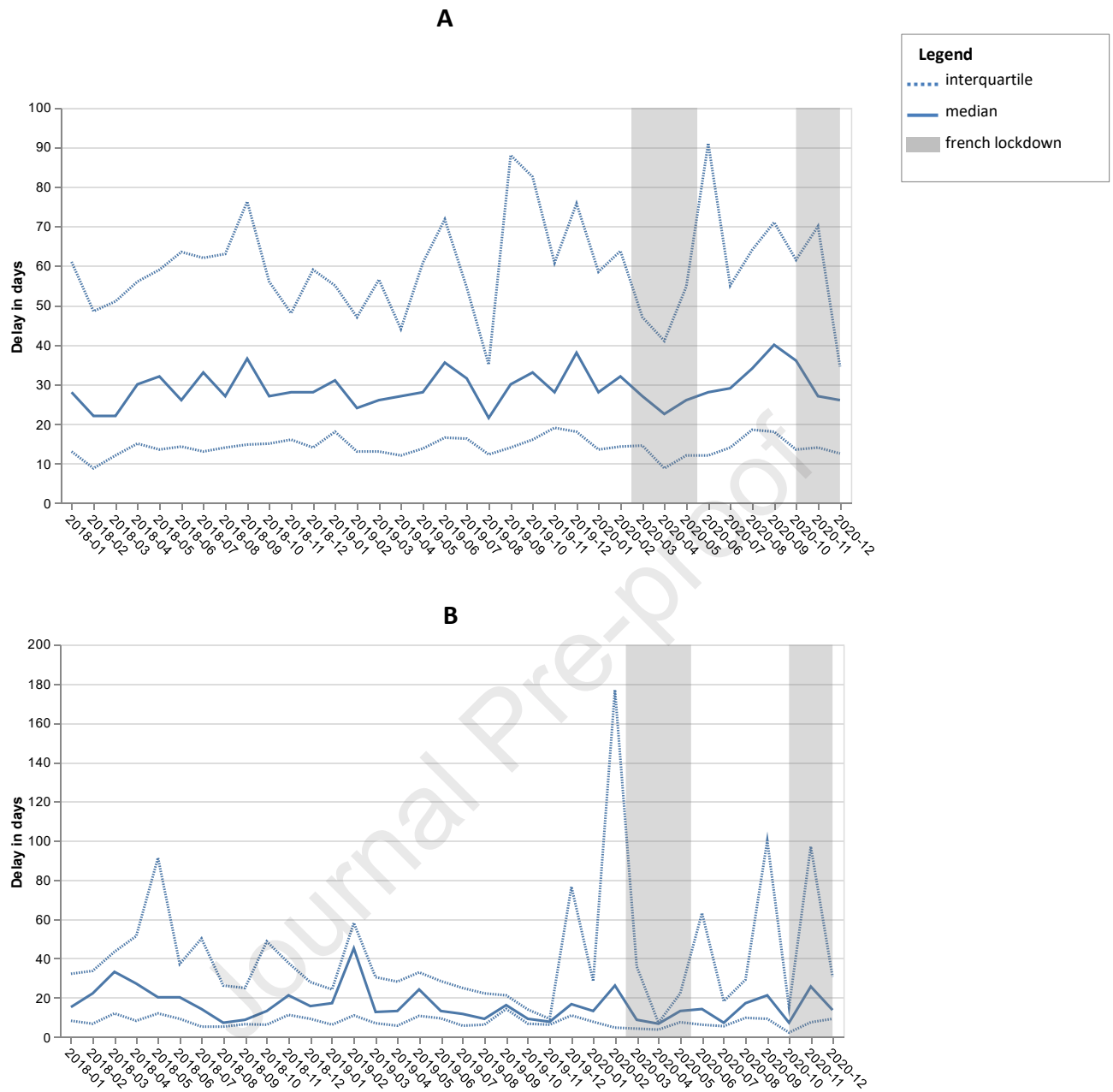


Figure 2. Evolution of the median delay between the 1st multidisciplinary tumor board (MTB) and the 1st therapeutic procedure for patients newly referred to the AP-HP hospitals between 2018 and 2020 for a lung cancer: patients for whom anticancer treatment was initiated before (2.A) (n=2,507, 77%) or after (2.B) MTB (n=736, 23%).

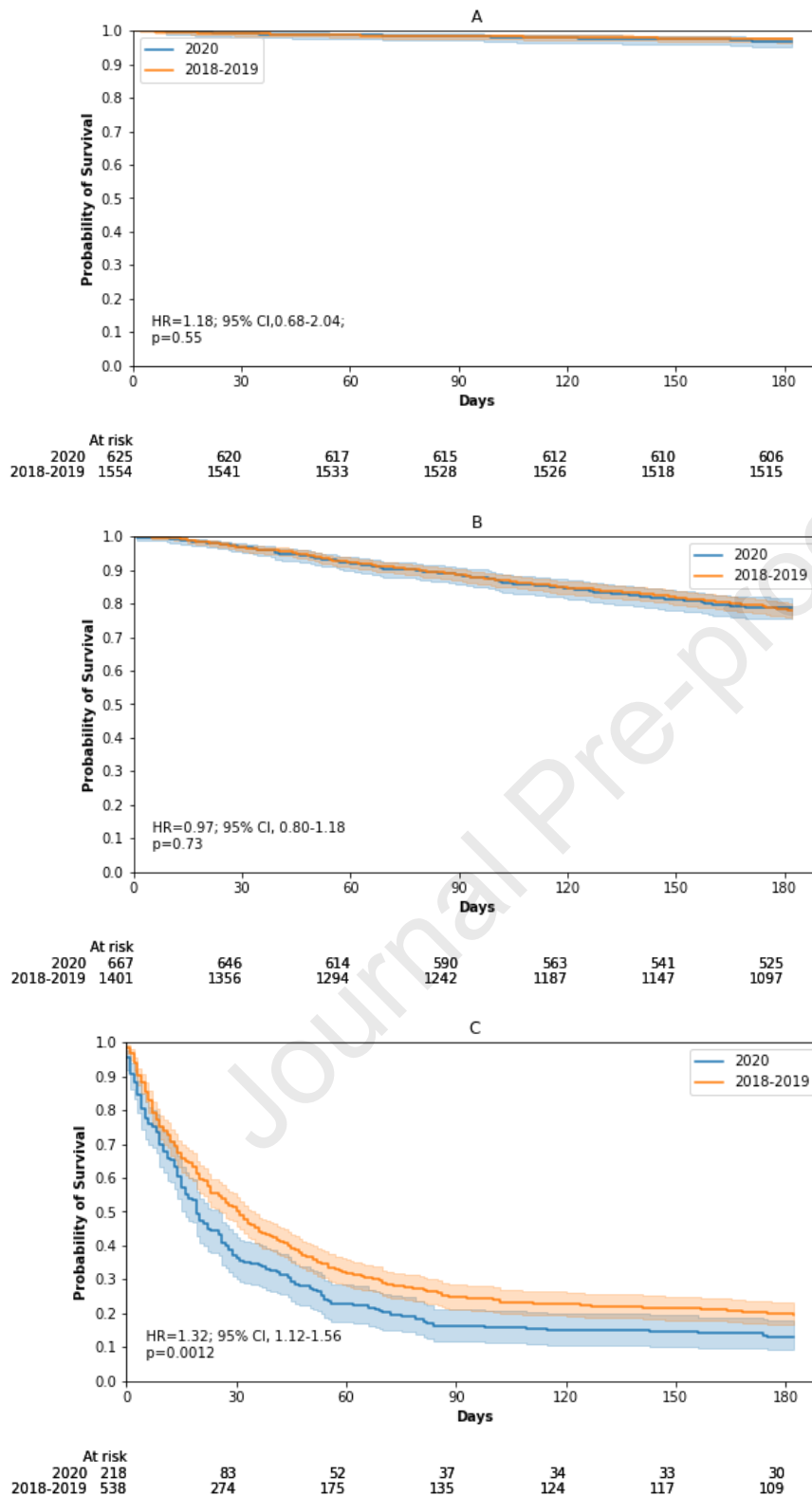


Figure 3. Six-month overall survival rates of newly referred lung cancer patients undergoing upfront tumor resection (3.A), anticancer systemic therapy (3.B) or best supportive care (3.C) in 2018-2019 and in 2020 at AP-HP University hospitals and hazard ratio (HR) estimated by a Cox proportional hazard model.

Highlights

- During the 1 st SARS-CoV2 lockdown, the number of new lung cancers decreased by 32%
- In 6,240 cases, initial tumor stage, treatment categories did not vary (2018–2021)
- Delay between multidisciplinary boards and cancer treatments did not vary over time
- Overall survival of patients diagnosed after the outbreak did not impair
- COVID was associated with poorer OS in patients with systemic anticancer therapy

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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